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# Sedentary Time and the Cumulative Risk of Preserved and Reduced Ejection Fraction Heart Failure: from the Multi-Ethnic Study of Atherosclerosis

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**SEDENTARY TIME AND CUMULATIVE RISK OF PRESERVED AND  
REDUCED EJECTION FRACTION HEART FAILURE: FROM THE  
MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS**

By

Brandi Scot Rariden

A thesis submitted to the Department of Clinical and Applied Movement Sciences

in partial fulfillment of the requirements for the degree of

Master of Science in Health, Exercise Science and Chronic Disease

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BROOKS COLLEGE OF HEALTH

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### **Dedication and Acknowledgements**

This thesis is dedicated to my daughters, Joscelyn, Scarlet, and Peyton. It is your love for life and passion for knowledge that inspires me to continuously strive to be a better mother, student, and person. I only hope that every small goal that I accomplish further encourages each of you to discover your own passions and dreams, set your own goals, crush them, and then set bigger ones. I am incredibly proud of all of you. It is also dedicated to my wonderful husband, Justin. Absolutely none of this would be possible without your patience, understanding, encouragement, and untiring support. You have held down the fort and pulled more than your share of the weight these past few years, and I am beyond grateful for it all. No matter how many chapters I publish in life, you four will always be my best.

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**Nomenclature**

cm	centimeter
d/wk	days per week
hr/week	hours per week
kg/m <sup>2</sup>	kilograms per meter squared
MET·min·wk <sup>-1</sup>	MET minutes per week
min/wk	minutes per week

**List of Abbreviations**

AHA	American Heart Association
BMI	body mass index
CI	confidence interval
CVD	cardiovascular disease
CHD	coronary heart disease
CHF	congestive heart failure
DHF	diastolic heart failure
EF	ejection fraction
FHS	Framingham Heart Study
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrfEF	heart failure with reduced ejection fraction
HTN	hypertension
HRs	hazard ratios
LTPA	leisure-time physical activity
LV	left ventricle/left ventricular
LVEF	left ventricular ejection fraction
MESA	Multi-Ethnic Study of Atherosclerosis
MET	metabolic equivalent
MI	myocardial infarction
nH	non-Hispanic
PA	physical activity

SAS	statistical analysis software
SHF	systolic heart failure
ST	sedentary time
TWPAS	typical week physical activity survey
WC	waist circumference

## ABSTRACT

- Purpose:** The purpose of this study was to examine the relationship between self-reported sedentary time (ST) and the cumulative risk of preserved ejection fraction heart failure (HFpEF) and reduced ejection fraction heart failure (HFrEF) using a diverse cohort of U.S. adults 45-84 years of age.
- Methods:** Using data from the Multi-Ethnic Study of Atherosclerosis (MESA), we identified 6,814 subjects (52.9% female). All were free of baseline cardiovascular disease. Cox regression was used to calculate the hazard ratios (HR) associated with baseline ST and risk of overall heart failure (HF), HFpEF, and HFrEF. Weekly self-reported ST was dichotomized based on the 75<sup>th</sup> percentile (1,890 min/wk).
- Results:** During an average of 11.2 years of follow-up there were 178 first incident HF diagnoses; 74 HFpEF, 69 HFrEF and 35 with unknown EF. Baseline ST >1,890 min/wk was significantly associated with an increased risk of HFpEF (HR [95% CI]; 1.87 [1.13 – 3.09],  $p = 0.01$ ), but not HFrEF (HR [95% CI]; 1.30 [0.78 – 2.15],  $p = 0.32$ ). The relationship with HFpEF remained significant in separate fully adjusted models including either waist circumference (HR [95% CI]; 2.16 [1.23 – 3.78],  $p < 0.01$ ) or body mass index (HR [95% CI]; 2.17 [1.24 – 3.80],  $p < 0.01$ ). Additionally, every 60 minute increase in weekly ST was associated with a significant 3% increased risk of HFpEF (HR [95% CI]; 1.03 [1.01 – 1.05],  $p < 0.01$ ).
- Conclusions:** Sedentary time > 1,890 min/wk (~ 4.5 h/d) is a significant independent predictor of HFpEF, but not HFrEF.

## **Chapter One: Introduction**

Heart failure (HF) is a chronic, progressive condition in which the myocardium is unable to pump enough blood through circulation to meet the body's needs (1). It is highly prevalent in older adults living in the United States (U.S.) (2, 3) and around the world (4, 5) and is accompanied by a very poor prognosis (2, 6-9). Heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) are two recognized subtypes of HF with independent pathophysiological pathways and risk factors (10, 11). Sedentary time (ST) has been shown to have a positive relationship with overall HF incidence, independent of multiple common risk factors, including physical activity (PA) (12).

This chapter provides an overview of relevant background information and epidemiology pertaining to both HF and ST. A focused literature review on existing knowledge regarding the relationship between these two topics is also included. It concludes with the purpose and significance of this research, including the specific questions addressed, and a description of the project. The limitations inherent to the study design are also listed.

## **BACKGROUND**

### ***HEART FAILURE***

According to 2017 estimates, the prevalence of HF among U.S. adults >20 years of age is currently 6.5 million (2). By 2030, this number is projected to reach 8.5 million, an increase of 46% from the 2012 estimates (3). Globally, based on 2014 estimates, HF affects at least 26 million people around the world (4). At 45 years of age, the lifetime risk of developing HF ranges from 20-45% (6). Presently, the HF prognosis is extremely

poor; approximately 50% of people receiving a HF diagnosis will die within five years (7, 8). In the Atherosclerosis Risk in Communities Study (13), the 30-day and 1-year case fatality rates after hospitalization for HF were 10.4% and 22%, respectively. One in eight deaths mentions HF on the death certificate and the number of deaths attributable to HF has remained mostly unchanged since 1995 (9). Despite the advances in health care and medication, the mortality and morbidity rates associated with HF remain high, while the quality of life remains poor.

In the American Heart Association (AHA)/American College of Cardiology guidelines (14, 15), HF is defined as a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood. As such, HF has been classified according to anatomical location (left-sided or right-sided), etiology (systolic or diastolic), and contractile function (preserved or reduced ejection fraction). However, pure right-sided heart failure is uncommon; the most common cause of right-sided heart failure is left-sided heart failure (16-18).

Furthermore, although congestive heart failure (CHF) has historically been used interchangeably with generalized HF, CHF is defined as a worsened state of HF in which fluid has backed up into the lungs and peripheral tissues (1). Since not all patients have volume overload at the time of initial or subsequent evaluation, the term heart failure is preferred over CHF (15). Most recently, left ventricular ejection fraction, the percentage of blood that is pumped from the left ventricle, has been used to differentiate between the two different subtypes of left-sided HF. The demarcation points and descriptions of these two subtypes are presented in Table 1.

<b>Table 1. Heart Failure Classification by Ejection Fraction</b>		
<b>Classification</b>	<b>Ejection Fraction</b>	<b>Description</b>
I. Heart Failure with Reduced Ejection Fraction (HFrEF)	$\leq 40\%$	Traditionally referred to as systolic HF. It is only in these patients that efficacious therapies have been demonstrated.
II. Heart Failure with Preserved Ejection Fraction (HFpEF)	$\geq 50\%$	Traditionally referred to as diastolic HF. To date, efficacious therapies have not been identified.
IIa. HFpEF, borderline	41-49%	These patients fall into the borderline group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HFpEF.

*Note.* Adapted from “ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines” by Yancy et al. *Circulation*. 2013;128(16):1810-52.

According to Yancy et al (19), HFrEF is defined as an EF  $\leq 40\%$ , HFpEF is an EF  $\geq 50\%$ , and an EF of 41-49% is classified as borderline HFpEF. These are the cut points that the AHA also provides (1). This differential diagnosis based on EF is crucial as previous research has demonstrated that in addition to having different risk factors and pathophysiology, the prognosis and response to pharmacological treatment and rehabilitative therapy are also different among these subgroups (10, 11, 20-22). Presently, therapeutic strategies that are successful in improving symptoms among those with HFrEF (i.e. angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, beta blockers) have proven ineffective on patients with HFpEF (20-22).

Additionally, while the current prevalence of HFpEF compared to HFrEF is similar (47% HFpEF and 53% HFrEF), the hospitalization rate for HFpEF is increasing; the average prevalence of HFpEF hospitalizations increased from 38% to 54% in a 15-year time span (22). Furthermore, racial and gender differences in the prevalence of HF



subtypes exist, with black males having the highest proportion of hospitalized HFrEF (70%) and white females having the highest proportion of hospitalized HFpEF (59%) (23).

Several risk factors for overall HF have been identified. Common significant reoccurring risk factors include coronary heart disease (CHD), hypertension (HTN), diabetes, smoking, male gender, valvular heart disease, possessing less than a high school education, low PA participation, and obesity (24-26). As previously mentioned, these variables are not all significant predictors when HF is investigated independently by HFpEF and HFrEF (10, 11, 20-22).

### ***SEDENTARY TIME***

Sedentary behavior has been defined as any waking behavior characterized by an energy expenditure  $\leq 1.5$  metabolic equivalents (METs), while in a sitting, reclining or lying posture (27). Therefore, ST is the total amount of time spent engaging in sedentary behaviors. This is distinctly different from physical inactivity, defined as an insufficient amount of PA to meet present PA recommendations (28). It is possible to meet the PA guidelines and still accumulate large amounts of ST. A 2013 systematic review (29) reported that almost 60% of older adults report sitting for more than 4 hours per day, and when ST was objectively measured via accelerometer, it was found that 67% of the population are sedentary for more than 8.5 hours in their waking day. Another study by Harvey et al. (30), found that time spent sedentary ranges from 5.3–9.4 hours per waking day in older adults. A study utilizing a time-lapse camera and activity monitors in older

adults found that participants appeared to frequently have vacant (non-screen) sitting time (41% of total ST), however, screen ST was also prevalent (36% of total ST) (31).

Sedentary time has been shown to have a positive, dose-response association with mortality from all-causes and cardiovascular disease (CVD), independent of leisure time PA (32, 33). Additionally, a 2015 meta-analysis (34) of 47 studies also concluded that self-reported prolonged ST was significantly associated with CVD incidence and CVD mortality (HR, 1.14 [CI, 1.00 to 1.73] and 1.15 [CI, 1.11 to 1.20], respectively) independent of PA. When examined as a continuous variable, each hour per day of sitting time was associated with 2% greater risk of CVD (HR, 1.02 [CI 1.01 to 1.03] and each MET-hour per week of PA with a 1% lower risk of CVD (HR, 0.990 [CI, 0.987 to 0.992]) (35). The AHA recently released a science advisory stating that the risk of adverse CVD and diabetes mellitus outcomes associated with sedentary behavior must be quantified in order for specific sedentary behavior guidelines to be established (36).

## **FOCUSED LITERATURE REVIEW**

The evidence suggests that a significant association exists between increased PA and decreased incidence of HF (37). A study by Pandey et al. (10) concluded that there is a strong, dose-dependent association between PA levels, body mass index (BMI), and risk of HF. When these investigators compared HF subtypes, higher PA levels and lower BMI were more consistently associated with a lower risk of HFpEF compared with HFrEF. Presently, there are a scarce number of studies that have examined the relationship between ST and HF risk. In a study by Wijndaele et al. (12), television viewing in hours per day was positively associated with incident HF, independent of age,

gender, education, smoking, alcohol, hypertension, dyslipidemia, antidepressant medication use, baseline diabetes status, family history of CVD, sleep duration and total PA. However, there is a paucity of research regarding the relationship between ST and the HF subtypes.

## **PURPOSE AND SIGNIFICANCE**

In light of the poor prognosis associated with both forms of HF and the limited treatment options currently available for HFpEF, it is vital that more research is conducted to examine the individual risk factors associated with each class of HF to be able to target better preventive and therapeutic strategies. Therefore, the purpose of this study was to examine the relationship between self-reported ST and the cumulative risk of HFpEF and HFrEF using a diverse, population-based sample of U.S. adults. The specific research questions that were addressed include:

1. Is there an association between a higher volume of total ST and the cumulative risk of HF, HFrEF, or HFpEF?
2. If a relationship does exist, does the relationship remain significant following adjustment for:
  - a. Demographics and traditional risk factors
  - b. Physical activity
  - c. Adiposity measures (waist circumference and body mass index)

## PROJECT DESCRIPTION

This secondary analysis used data from the Multi-Ethnic Study of Atherosclerosis (MESA) (38). The MESA consists of a population-based sample of 6,814 men and non-pregnant women aged 45-84, who were free of cardiovascular disease at baseline. The proportional hazards regression procedure (PROC PHREG) was utilized to calculate multivariable adjusted hazard ratios (HRs) to determine risk of HFpEF and HFrEF according to baseline, self-reported ST. Separate regression models were constructed for both subtypes of HF to test the relationship between several variables commonly associated with HFpEF and HFrEF. This study was not without limitations:

1. The use of self-reported baseline ST is subject to recall and self-report bias.  
Additionally, ST was not objectively measured.
2. The time to the first HF event was used to establish incident HF and EF, therefore subsequent HF events by the same participant or changes in EF measurement over time were not included in the analysis.
3. Baseline ST and PA were examined for all participants, changes in behavior over the timeframe of the study were not taken into consideration for risk determination.
4. Individuals without EF data at the time of the first HF event were not included in the analysis.

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## **Chapter Two: Review of Literature**

Heart failure (HF) refers to a complex syndrome that encompasses many cardiac disorders that ultimately result in either one or both ventricles of the heart being unable to fill or eject blood properly (1). Cardinal symptoms of HF include dyspnea, fatigue, and fluid retention (2). As the heart is a very adaptive organ, the failure of the ventricles to work efficiently is usually the product of long term compensation of the myocardium to overcome a multitude of other potential underlying problems (i.e. hypertension (HTN), coronary artery disease (CAD), myocardial infarction, inflammation, and ischemia). Although HF is a chronic condition, symptoms can present acutely and progress quickly if untreated. Right-sided HF refers to HF in which the right chambers of the heart are affected. However, pure right-sided HF is uncommon; in fact, the most common cause of right-sided HF is left-sided HF (3-5). Furthermore, the majority of patients with left-sided HF have symptoms due to left ventricular (LV) myocardial dysfunction (6).

Left ventricular ejection fraction (EF) is a measurement of the amount of blood that is ejected from the LV with each beat relative to the amount of blood present at the end of the diastole. This diagnostic tool is used to differentiate between two types of left-sided HF: HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). According to the American Heart Association (AHA) (2), HFrEF is defined as an  $EF \leq 40\%$ , HFpEF is an  $EF \geq 50\%$ , and an EF of 41-49% is considered borderline HFpEF. The pathophysiological mechanisms that lead to these two subtypes of HF are different, multidimensional, and not fully understood at this time.

Traditionally, epidemiologic research involving HF was conducted investigating the relationship between potential risk factors and HF as one singular outcome. As knowledge of the different comorbidities and characteristics of patients with HFrEF and

HFrEF unfolded, investigators began examining the potential risk predictors of HFrEF and HFpEF independently (7). This led to the identification of differences in risk factors for each of these HF subtypes (8-13), suggesting differing etiologies.

This chapter includes a focused history on the terminology of HFrEF and HFpEF, an overview of the pathophysiological mechanisms related to each of these subtypes, and a summary of the known risk factors independently associated with them. Additionally, existing knowledge about the relationship between sedentary time (ST) and HF is included, along with several synopses of previous research studies conducted involving the HF subtypes. It concludes with a summary of the literature and the explanation of the need for additional research.

## **TERMINOLOGY**

Previously, the terms systolic and diastolic were primarily used to categorize HF, based on the phase of the cardiac cycle in which dysfunction occurred and differences in clinical presentation. In 2006, van Heerebeek et al. (7) investigated the distinction between systolic heart failure (SHF) and diastolic heart failure (DHF) by comparing LV myocardial structure and function using endomyocardial biopsy samples of patients with known SHF and DHF. Distinct cardiomyocyte abnormalities and LV remodeling were found to be present in each type of HF, which supported the clinical separation of HF patients into these SHF and DHF phenotypes. Work by Katz et al. (14) illustrated that patients with SHF had eccentric LV hypertrophy, evident by a low LV wall mass-volume ratio, whereas patients with DHF presented with concentric LV hypertrophy or a higher LV wall mass-volume ratio.

The terms HFrEF and HFpEF were commonly used interchangeably with SHF and DHF, respectively. However, because abnormalities of systolic and diastolic LV dysfunction were found to coexist regardless of EF, SHF and DHF are no longer the common vernacular (15-17). The terms HFrEF and HFpEF are currently recommended by the AHA and described as being a more accurate way to categorize HF patients (2). This is further supported by several studies that have observed differing patient demographics, risk factors, comorbid conditions, prognosis, and therapeutic responses based on EF (8-13, 18). The Heart Failure and Echocardiography Associations of the European Society of Cardiology (19) also stated that structural, functional, and molecular biological arguments support the theory that clinical HF presents and evolves not as a single syndrome, but as two independent syndromes, one with reduced LVEF and the other with a preserved “normal” EF.

## **DIAGNOSIS**

The diagnosis of HF is largely clinical and based on a thorough medical history and physical exam. The 2009 focused AHA guidelines (1) stated that three fundamental questions must be addressed in the diagnosis of HF:

- 1) Is the LVEF preserved or reduced?
- 2) Is the structure of the LV normal or abnormal?
- 3) Are there other structural abnormalities such as valvular, pericardial, or right ventricular abnormalities that could account for the clinical presentation?

The diagnosis of HFpEF is often more complex, as it typically involves a more thorough process of eliminating other potential cardiac disorders to ensure an accurate diagnosis. The most recent guidelines from the AHA (20) stated that in practice, the diagnosis of HFpEF is based on meeting the following three requirements:

- 1) Clinical signs or symptoms of HF
- 2) Evidence of preserved or normal EF
- 3) Evidence of abnormal LV diastolic dysfunction that can be determined by Doppler echocardiography or cardiac catheterization

### **PATHOPHYSIOLOGY**

As previously stated, significant evidence exists supporting the development of HFrEF and HFpEF as two complex syndromes. They have overlapping risk factors and possess similar clinical presentations, but consist of different pathologic myocardial remodeling pathways that result in opposing structural and functional abnormalities. Myocardial remodeling is used to describe a variety of changes in the biophysiology of the cardiomyocyte, the volume and composition of cardiomyocyte and noncardiomyocyte compartments, and the geometry and architecture of the LV chamber that occur in response to myocardial infarction, pressure or volume overload, cardiomyopathic states, and exposure to infectious or cardiotoxic agents (21). The complete pathological pathways that result in HFpEF and HFrEF are not currently completely understood, but a few well supported hypotheses have been proposed.

### ***HFrEF***

For HFrEF, the main drivers of myocardial remodeling are a progressive loss of cardiomyocytes resulting from cell autophagy, apoptosis, or necrosis. This cell death is often the result of ischemia, infection, or toxicity that increases reactive oxygen species causing oxidative stress (22). These cells are then replaced with fibrous tissue. This type of remodeling typically results in an enlarged LV cavity that has thin, weak walls with patchy fibrous areas and consequently reduced pumping ability. Although the size of the cavity is enlarged and ventricular filling is not affected, the force of contraction the myocardium is able to generate is greatly diminished. This type of cardiac hypertrophy is typically referred to as eccentric hypertrophy.

### ***HFpEF***

In contrast, concentric hypertrophy is characteristically observed in HFpEF which results in a thick, stiff LV wall and a reduced cavity size. While the overall EF is preserved, a reduction in the absolute volume of blood ejected with each beat, or stroke volume, is significantly reduced. While the theories behind the drivers of HFpEF are less understood, the consensus appears to be that it is linked to endothelial inflammation. Inflammation has been linked to HFpEF, but not HFrEF in several previous studies (23-25). Chronic systemic inflammation affects not only the myocardium, but also other organs such as lungs, skeletal muscles, and kidneys (26). It also affects the renal microcirculation and the ability of the kidneys to excrete sodium, which contributes to the progressive fluid retention observed during transition from chronic compensated to acute decompensated HFpEF (26).



In 2013, Paulus et al. (22) proposed a new paradigm for the development of HFpEF which identified a systemic proinflammatory state induced by comorbidities as the cause of myocardial structural and functional alterations. The new paradigm presumed the following sequence of events in HFpEF: 1) a high prevalence of comorbidities such as overweight/obesity, diabetes mellitus, chronic obstructive pulmonary disease, and salt-sensitive hypertension induce a systemic proinflammatory state; 2) a systemic proinflammatory state causes coronary microvascular endothelial inflammation; 3) coronary microvascular endothelial inflammation reduces nitric oxide bioavailability, cyclic guanosine monophosphate content, and protein kinase G (PKG) activity in adjacent cardiomyocytes; 4) low PKG activity favors hypertrophy development and increases resting tension because of hypophosphorylation of titin; and 5) both stiff cardiomyocytes and interstitial fibrosis contribute to high diastolic LV stiffness and heart failure development.

### ***SUMMARY***

In summary, in HFrEF, myocardial remodeling is driven by cardiomyocyte death due to oxidative stress originating in the cardiomyocytes as a result of ischemia, infection, or toxicity. In HFpEF, comorbidities contribute to a systemic inflammatory state, which induces oxidative stress in the coronary microvascular endothelium. The location of the oxidative stress dictates the type of remodeling that occurs. In HFrEF, eccentric hypertrophy is often observed and in HFpEF, concentric hypertrophy. Understanding these pathways and main drivers is critical, as it allows for a better understanding of potential preventative and therapeutic approaches. This is especially important for HFpEF due to the lack of current successful treatment options.

## **RISK FACTORS**

Several prospective cohort studies have investigated the relationship between potential risk factors and incident HFpEF and HFrEF (8-11). A summary of these studies is presented in Table 1. Only risk factors that were significant in the fully-adjusted models are provided. The lack of consistent findings is likely a result of the differences in sample characteristics, definitions of HFpEF and HFrEF, and study designs.

**Table 1. Studies Reporting Significant Risk Factors for HFpEF and HFrEF**

Year	Title	Authors	Dataset Years	EF Definitions (n)	Significant HFpEF risk factors	Significant HFrEF risk factors
2009	Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction (8)	Lee, Gona, Vasan, Larson, Benjamin, Wang, Tu, Levy	FHS 1981-2004	HFpEF > 45% (n=220) HFrEF ≤ 45% (n=314)	HTN Female Gender	CHD
2013	Predictors of new-onset heart failure: differences in preserved versus reduced ejection fraction (9)	Ho, Lyass, Lee, Vasan, Kannel, Larson, Levy	FHS 1981-2008	HFpEF > 45% (n=196) HFrEF ≤ 45% (n=261)	Age Diabetes Valvular Disease BMI Smoking A-Fib	Age Diabetes Valvular Disease Male Gender Total Cholesterol HR HTN CVD LVH LBBB
2013	Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND (10)	Brouwers, de Boer, van der Harst, Voors, Gansevoort, Bakker, Hillege, van Veldhuisen, van Gilst	PREVEND IT 1998-2010	HFpEF ≥ 50% (n=125) HFrEF ≤ 40% (n=241)	Age NT-proBNP Female Gender A-Fib UAE Cystatin C	Age NT-proBNP Male Gender Smoking Troponin T Interim MI
2016	Impact of race, ethnicity, and multimodality biomarkers on the incidence of new-onset heart failure with preserved ejection fraction (11)	Silverman, Patel, Blankstein, Lima, Blumenthal, Nasir, Blaha	MESA 2000-2012	HFpEF ≥ 45% (n=111) HFrEF < 45% (n=107)	BMI LVH Troponin T Age HTN Diabetes Interim MI NT-proBNP LV mass index	HR Smoking eGFR Age HTN Diabetes Interim MI NT-proBNP LV mass index

Abbreviations: HFpEF= heart failure with preserved ejection fraction; HFrEF= heart failure with reduced ejection fraction; EF= ejection fraction; FHS= Framingham Heart Study; HTN= hypertension; CHD= coronary heart disease; BMI= body mass index; A-Fib= atrial fibrillation; HR= heart rate; CVD= cardiovascular disease; LVH= left ventricular hypertrophy; LBBB= left bundle branch block; NT-proBNP= N-terminal pro-brain natriuretic peptide; UAE= urinary albumin excretion; MI= myocardial infarction; MESA= Multi-Ethnic Study of Atherosclerosis; eGFR= estimated glomerular filtration rate; LV= left ventricle; PREVEND IT= The Prevention of Renal and Vascular Endstage Disease Intervention Trial.

Lee et al. (8) were one of the first groups to examine antecedent clinical variables in participants who went on to develop HFpEF (EF > 45%) and HFrEF (EF ≤ 45%).

Using data from 314 participants in the Framingham Heart Study (FHS) who had incident HF occurring between 1981 and 2004, they examined the age and sex adjusted odds of risk factors associated with HFpEF versus HFrEF. The authors found that coronary heart disease was associated with significantly reduced odds of HFpEF (Odds ratio (OR), 0.38 [CI, 0.27-0.55]). In contrast, female gender and hypertension significantly increased odds of HFpEF (OR, 2.55 [CI 1.77-3.68]; OR, 2.13 [CI, 1.43-3.23], respectively).

In 2013, Ho et al. (9) examined the predictors of incident HFpEF and HFrEF also using data from 6,340 participants ( $60 \pm 12$  years) who participated in the FHS between 1981 and 2008. After a mean follow-up of 7.7 years, 196 participants developed HFpEF ( $EF > 45\%$ ) and 261 developed HFrEF ( $EF \leq 45\%$ ). Age, diabetes, and valvular disease were found to be significant predictors of both subtypes. Higher BMI, smoking, and atrial fibrillation were significantly associated with HFpEF, whereas male gender, cholesterol, heart rate, hypertension, cardiovascular disease, LV hypertrophy, and left bundle branch block were all associated with HFrEF.

Brouwers et al. (10) investigated the prediction of new onset HFpEF compared with HFrEF using data from 8,592 participants (28-75 years) who participated in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study. After a median follow-up of 11.5 years, 125 participants developed HFpEF ( $EF \geq 50\%$ ) and 241 developed HFrEF ( $EF \leq 40\%$ ). The investigators found that age, female gender, history of atrial fibrillation, increased urinary albumin excretion, and cystatine C were all significantly associated with HFpEF. In contrast, male gender, smoking, increased N-terminal pro-brain-type natriuretic peptide, and increased highly sensitive troponin T were associated with HFrEF.

Silverman et al. (11) identified various significant risk factors for HFrEF and HFpEF using data from 6,814 Multi-Ethnic Study of Atherosclerosis (MESA) participants aged 45-84 years. Proportional hazard regression models were used to identify the relationship between baseline characteristics and incident HFrEF and HFpEF. Variables that maintained significance in multivariable adjusted analysis for HFpEF and HFrEF are listed in adapted Table 2 and Table 3, respectively (11). Variables that did not make a significant contribution in the multivariable analyses are not provided.

<b>Table 2. Significant Multivariable Adjusted Risk Factors for HFpEF</b>				
<b>Variable</b>	<b>Unadjusted HR (95% CI)</b>	<b>p-value</b>	<b>Multivariable Adjusted HR (95% CI)</b>	<b>p-value</b>
<b>Age (per SD)</b>	2.33 (1.91–2.86)	<0.001	2.27 (1.72–3.01)	<0.001
<b>Black Race</b>	0.69 (0.42–1.12)	0.132	0.46(0.26–0.82)	0.009
<b>Hypertension</b>	3.44 (2.26–5.23)	<0.001	1.81 (1.14–2.90)	0.013
<b>Body Mass Index (per SD)</b>	1.27 (1.09–1.49)	0.002	1.35 (1.08–1.68)	0.009
<b>Diabetes</b>	3.42 (2.29–5.11)	<0.001	2.33 (1.47–3.71)	<0.001
<b>LVH by ECG</b>	5.00 (2.01–12.44)	0.001	4.33 (1.70–11.04)	0.002
<b>Interim MI</b>	6.66 (3.91–11.34)	<0.001	4.80 (2.67–8.62)	<0.001
Abbreviations: HFpEF= heart failure with preserved ejection fraction; HR= hazard ratio; CI= confidence interval; SD= standard deviation; LVH= left ventricular hypertrophy; ECG= electrocardiogram; MI= myocardial infarction.				

*Note.* Adapted from “Impact of Race, Ethnicity, and Multimodality Biomarkers on the Incidence of New-Onset Heart Failure With Preserved Ejection Fraction (from the Multi-Ethnic Study of Atherosclerosis)” by Silverman et al. *The American Journal of Cardiology*. 2016;117(9):1474-81.

<b>Table 3. Significant Multivariable Adjusted Risk Factors for HFrEF</b>				
<b>Variable</b>	<b>Unadjusted HR (95% CI)</b>	<b>p-value</b>	<b>Multivariable Adjusted HR (95% CI)</b>	<b>p-value</b>
<b>Age (per SD)</b>	1.72 (1.44–2.07)	<0.001	1.30 (1.00–1.70)	0.048
<b>Female</b>	0.34 (0.23–0.53)	<0.001	0.34 (0.21–0.56)	<0.001
<b>Chinese</b>	0.08 (0.01–0.58)	0.013	0.14 (0.02–1.00)	0.05
<b>Heart Rate (per SD)</b>	1.26 (1.04–1.53)	0.019	1.25 (1.03–1.51)	0.022
<b>Hypertension</b>	3.26 (2.14–4.97)	<0.001	2.04 (1.23–3.36)	0.003
<b>Current Smoking</b>	1.68 (1.04–2.70)	0.034	2.00 (1.19–3.36)	0.009
<b>Diabetes</b>	2.87 (1.88–4.38)	<0.001	1.84 (1.13–3.00)	0.014
<b>eGFR (per SD)</b>	1.60 (1.29–1.99)	<0.001	1.29 (1.04–1.59)	0.019
<b>Interim MI</b>	4.81 (2.65–8.71)	<0.001	2.56 (1.32–4.97)	0.005
<b>NT-proBNP &gt; 75<sup>th</sup> percentile</b>	5.11 (3.27–7.98)	<0.001	5.00 (2.70–9.25)	<0.001
<b>LV mass index (per SD)</b>	1.88 (1.59–2.22)	<0.001	1.94 (1.68–2.25)	<0.001
Abbreviations: HFrEF= heart failure with reduced ejection fraction; HR= hazard ratio; LV= left ventricular; NT-proBNP= N-terminal pro-brain natriuretic peptide; MI= myocardial infarction; eGFR= estimated glomerular filtration rate; LV= left ventricular; SD= standard deviation.				

*Note.* Adapted from “Impact of Race, Ethnicity, and Multimodality Biomarkers on the Incidence of New-Onset Heart Failure With Preserved Ejection Fraction (from the Multi-Ethnic Study of Atherosclerosis)” by Silverman et al. *The American Journal of Cardiology*. 2016;117(9):1474-81.

### **HF and SEDENTARY TIME**

Sedentary behavior has been defined as any waking behavior characterized by an energy expenditure  $\leq 1.5$  metabolic equivalents (METs), while in a sitting, reclining or lying posture (27). Therefore, sedentary time (ST) is the total amount of time spent engaging in sedentary behaviors. This is distinctly different from physical inactivity,

defined as an insufficient amount of PA to meet present PA recommendations (28). It is possible to meet the PA guidelines and still accumulate large amounts of ST. Sedentary time has been shown to have a positive, dose-response association with mortality from all-causes and cardiovascular disease (CVD), independent of leisure time PA (29, 30). Additionally, a 2015 meta-analysis (31) of 47 studies also concluded that self-reported prolonged ST was significantly associated with CVD incidence and CVD mortality (HR, [95% CI]; 1.14 [ 1.00 - 1.73] and 1.15 [ 1.11 - 1.20], respectively) independent of PA. When examined as a continuous variable, each hour per day of sitting time was associated with 2% greater risk of CVD (HR [95% CI]; 1.02 [1.01 - 1.03] and each MET-hour per week of PA with a 1% lower risk of CVD (HR, [95% CI]; 0.99 [0.99 - 0.99]) (32).

Presently, there are a scarce number of studies that have examined the relationship between ST and HF risk. Young et al (33) examined the relationship between sedentary time and incident HF in 82,694 men 45 years of age and older from the California Men's Health Study. After 10 years of follow-up, 3,473 men developed HF. Controlling for sociodemographics, hypertension, diabetes, hyperlipidemia, body mass index, smoking, diet, and PA, those in the medium ST category (HR [95% CI]; 1.13 [1.04-1.24]) and the highest ST category (HR [95% CI]; 1.34 [1.21 – 1.48]) had significantly increased risk of HF compared to those in the lowest ST category.

Additionally, in a study by Wijndaele et al. (34), the investigators examined the association between television viewing time and incident HF in 12,608 men and women from the EPIC Norfolk Study. They found that television viewing (hours/day) was significantly associated with incident HF, independent of age and gender (HR [95%CI];

1.15 [1.05–1.25]), education, smoking, alcohol, hypertension, dyslipidaemia, antidepressant medication, baseline diabetes status, family history of CVD, sleep duration (HR [95%CI]; 1.11 [1.01–1.21]), and total PA (HR [95%CI]; 1.10 [1.01–1.20]). However, there is a paucity of research regarding the relationship between ST and the HF subtypes.

### **RELEVANT HFpEF/HFrEF RESEARCH**

Higher levels of physical activity (PA), high cardiorespiratory fitness, lack of obesity and low ST have all been shown to be associated with reductions in overall HF risk (27, 35-44). The relationship between these variables and the risk of HFpEF and HFrEF subtypes is less explored. This section highlights several studies that have investigated some of these relationships.

#### ***HFpEF/HFrEF AND PHYSICAL ACTIVITY***

Kraigher-Krainer et al. (45) evaluated an average of 10 years of follow-up data from 1,142 participants of the FHS. Participants answered questions about their PA participation via a questionnaire administered at baseline. Tertiles of PA were created based on total self-reported PA. Over the course of the study, 108 participants developed HFpEF and 106 HFrEF. In age- and sex-adjusted models, the middle and highest PA tertiles were associated with a significant 15-40% lower risk of HFrEF, and 41-66% lower risk of HFpEF, with a graded response across tertiles. In multivariable models, the association of higher PA with lower risk of HFPEF retained significance, whereas the significant association with HFREF was lost.



Pandey et al. (12) investigated the relationship between leisure time physical activity (LTPA) and risk of HFpEF and HFrEF using pooled data from three large, prospective, cohort studies; the Women's Health Initiative, the MESA, and the Cardiovascular Health Study. The total sample included 51,451 participants free of baseline HF. Participants were stratified into four different LTPA categories: 1) No LTPA; 2) 1 to <500 MET-min/week; 3) 500 to 1,000 MET-min/week; 4) >1,000 MET-min/week. After 645,515 person-years of follow-up, 3,180 HF events were observed, 1,252 HFpEF ( $\geq 45\%$  EF) and 914 HFrEF ( $< 45\%$  EF). Separate multivariable adjusted Cox proportional hazards models were created to determine the risk of HFpEF and HFrEF according to baseline LTPA and BMI category. Adjusted models revealed no significant associations between LTPA and HFrEF at any level. In contrast, HFpEF was found to have a significant dose-dependent association with LTPA levels (p for trend  $< 0.01$ ).

#### ***HFpEF/HFrEF AND OBESITY***

Ho et al. (9) and Silverman et al. (11) both observed a significant relationship between BMI and HFpEF, but not HFrEF. The study by Pandey et al. (12) investigated the relationship between BMI and risk of overall HF and its subtypes in detail. Participants were placed into five separate categories based on baseline BMI: 1) underweight; 2) normal weight (referent group); 3) overweight; 4) obese class I; and 5) obese class II-III. The investigators found that participants with a higher BMI (when compared to desirable BMI) had a positive, graded increase in risk of HFpEF, such that compared to normal weight participants, overweight, obese class I, and obese class II-III participants had 38%, 56%, and 172% higher risk of HFpEF, respectively. A significant

increase in risk for HFrEF was not observed in overweight, or obese class I individuals, only in obese class II-III. In linear contrast analysis, a significant dose-response association was found between BMI and HFpEF ( $p < 0.01$ ), but not HFrEF.

## SUMMARY

In summary, HFpEF and HFrEF are two subtypes of left-sided HF that have independent risk profiles and causal pathways. These causal pathways are typically driven by either several potential comorbidities that cause systemic inflammation, cardiac insult and cell death, or a combination of both. Depending on the original cause(s), differing patterns of cardiac remodeling occur, resulting in different structural and functional abnormalities. In the case of HFpEF, there are currently no effective therapeutic or pharmaceutical interventions available, therefore it is crucial to focus on identifying risk factors and prevention strategies. Additionally, HFpEF is more commonly associated with metabolic comorbidities, low levels of PA, and increased obesity than HFrEF. All of these are modifiable lifestyle risk factors that could be potential targets of prevention. As ST is also a modifiable lifestyle risk factor that has been shown to be associated with increased risk of HF, independent of PA, the examination of ST and the risk of HF subtypes is both warranted and necessary.

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## **Chapter Three: Methodology**

The purpose of this study was to examine the associations between sedentary time (ST) and the risk of overall heart failure (HF), heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF). If a relationship between any of these variables was observed, the secondary aim was to see if the relationship was maintained after controlling for:

- 1) Demographics and traditional risk factors
- 2) Physical activity (PA)
- 3) Adiposity measures (waist circumference [WC] and body mass index [BMI])

This section provides the details of the methodology that was used to address these research questions.

## **DATA COLLECTION**

This study utilized data from the Multi-Ethnic Study of Atherosclerosis (MESA), an ongoing population-based study sponsored by the National Heart Lung and Blood Institute of the National Institutes of Health. Details on this study have been published elsewhere (1). The sample (n= 6,814) consisted of men and women (45-84 years of age) who were free of baseline cardiovascular disease (CVD) upon enrollment. Participants were recruited from six different field centers at Universities across the United States:

- 1) University of California, Los Angeles, CA
- 2) University of Minnesota, St. Paul, MN
- 3) Northwestern University, Chicago, IL
- 4) Wake Forest University, Winston-Salem, NC
- 5) John Hopkins University, Baltimore, MD

- 6) Columbia University, New York, NY

MESA's exclusion criteria were:

- 1) Age younger than 45 or older than 84 years
- 2) Physician-diagnosed heart attack
- 3) Physician-diagnosed angina or taking nitroglycerin
- 4) Physician-diagnosed stroke or transient ischemic attack
- 5) Physician-diagnosed heart failure
- 6) Current atrial fibrillation
- 7) Having undergone procedures related to cardiovascular disease (CABG, angioplasty, valve replacement, pacemaker or defibrillator implantation, any surgery on the heart or arteries)
- 8) Active treatment for cancer
- 9) Pregnancy
- 10) Any serious medical condition which would prevent long-term participation
- 11) Weight >300 pounds
- 12) Cognitive inability as judged by the interviewer
- 13) Living in a nursing home or on the waiting list for a nursing home
- 14) Plans to leave the community within five years
- 15) Language barrier (speaks other than English, Spanish, Cantonese or Mandarin)
- 16) Chest CT scan in the past year

The MESA utilized both physical exams and questionnaires to examine the characteristics of subclinical CVD and the risk factors that predict progression to clinically overt CVD. The first exam took place from July 2000-July 2002, and a total of four additional follow-up exams were completed by 2012. Participants are continuously contacted every 9-12 months to assess clinical morbidity and mortality data.

The present study was reviewed and approved by the Institutional Review Board of the University of North Florida (Appendix A). Data from the MESA was requested and obtained from the National Institutes of Health/ National Heart, Lung, and Blood Institute: Biologic Specimen and Data Repository Information Coordinating Center (2). A copy of the signed research materials data agreement (RMDA) is provided in Appendix B.

### **PRIMARY DEPENDENT VARIABLE**

The primary outcome was time to congestive heart failure (TTCHF), classified as either definite or probable. Congestive heart failure (CHF) was an adjudicated event in MESA, determined by a panel of physicians following review of medical records. Probable CHF was defined as: CHF diagnosed by physician and patient receiving medical treatment for CHF. Definite CHF determination required evidence of pulmonary edema/congestion, dilated ventricle, poor left ventricular function, or evidence of left ventricular diastolic dysfunction. Those with an ejection fraction (EF)  $\leq 40\%$  at time of diagnosis were classified as HFrEF and those with an EF  $> 40\%$  were classified as HFpEF.

### PRIMARY INDEPENDENT VARIABLE

Self-reported baseline ST based on the typical week physical activity survey (TWPAS) completed by all MESA participants was the primary independent variable in this study.

The following questions from the TWPAS were used to estimate total weekly ST:

1. “In a typical week in the past month, did you sit or recline and watch TV?”
2. “In a typical week in the past month, did you read, knit, sew, visit, do nothing, non-work recreational computer?”

Responses included yes or no, days per week (1-7days), hours per day (1-5 or 5+ hours), and minutes per day (5, 15, 30, or 45 minutes). Total hours per day (converted to minutes) and minutes per day were summed and multiplied by days per week to accumulate estimated minutes per week of ST.

$$[(\text{HR/DAY} * 60 \text{ MN/HR}) + \text{MIN/DAY}] * \text{DAYS/WK} = \text{MIN/WK TOTAL ST}$$

This variable was then used to create two separate variables used in further analysis: SEDDICHOT, a variable dichotomized around the 75th percentile ( $\leq$  or  $>$  1,890 min/wk) and SEDHOURS, a variable that represented every 1 hour interval of weekly ST.

### OTHER INDEPENDENT VARIABLES

The potential confounding variables that were controlled for in this study included the following:

***AGE***

Age was self-reported on the personal history form at exam one. This was included in the analysis as a continuous controlling variable.

***SEX***

Sex was self-reported on the personal history form at exam one as either male or female.

***RACE***

Race was self-reported on the personal history form at exam one as either Caucasian, Chinese, African American, or Hispanic.

***SMOKING***

Smoking status was self-reported on the personal history form at exam one. The question stated, “Have you smoked cigarettes in the past 30 days?” Responses included yes or no.

***HYPERTENSION***

Self-reported based on the medical history form given at exam one. The question stated, “Has a doctor ever told you that you had high blood pressure or hypertension?” Responses included yes, no, or I don’t know. The response ‘I don’t know’ was recoded as a missing variable.

***DIABETES***

Self-reported based on the medical history form given at exam one. The question stated, “Has a doctor ever told you that you had Diabetes (sugar in blood)?” Responses included yes, no, or I don’t know. The response ‘I don’t know’ was recoded as a missing variable.



### ***METABOLIC SYNDROME***

Metabolic Syndrome was a calculated variable in MESA based on participants' measured waist circumference, triglycerides, high density lipoprotein cholesterol, blood pressure, and fasting blood glucose. The MESA utilized the National Cholesterol Education Program Guidelines (4) to define metabolic syndrome.

### ***PHYSICAL ACTIVITY***

An intentional physical activity variable was created in MESA that combined responses on the TWAPAS about time spent participating in the following activities (Questions 9-15):

- 1) Walking for exercise, pleasure, social reasons, walking during work breaks, and walking the dog is classified as intentional walking.
- 2) Dancing in church, ceremonies, or for pleasure.
- 3) Team sports such as softball, volleyball, basketball, or soccer.
- 4) Dual sports such as tennis, racketball, and paddleball.
- 5) Individual activities such as golf, bowling, yoga, or t'ai chi.
- 6) Moderate effort conditioning activities such as low impact aerobics, recreational (slow) bicycling, rowing on a rowing machine or in a lake, swimming in a pool or lake, or using weight lifting or conditioning machines at a health club.
- 7) Heavy effort conditioning activities such as high impact aerobics (e.g., Tai-bo, kick boxing, judo, karate), competitive or maximum effort running, bicycling, swimming, and work on health club machines.

### ***BODY MASS INDEX***

Body mass index was calculated as body weight in kilograms (kg) divided by height in meters squared ( $m^2$ ) using measurements obtained at exam one.

### ***WAIST CIRCUMFERENCE***

Waist circumference was measured at exam one in centimeters (cm).

## **STATISTICAL ANALYSIS**

Data was managed utilizing SAS 9.4 (3) where complex variable recodes, coding verification, and statistical analyses were performed. The means and frequency procedures (PROC MEANS and PROC FREQ) were used to construct a descriptive characteristics table for continuous and categorical variables, respectively. The univariate procedure (PROC UNIVARIATE) was used to determine the 75th percentile of self-reported ST.

Separate proportional hazards regression procedures (PROC PHREG) were utilized to calculate multivariable adjusted hazard ratios (HRs) to determine risk of overall HF, HFpEF and HFrEF according to baseline ST. Incident HF without data on ejection fraction were excluded from the HF subtype analysis. Five separate models were constructed for each of the outcome variables. Model one was unadjusted. Model two controlled for age, sex, race, smoking, hypertension, diabetes, and metabolic syndrome. Model three controlled for all variables in model two plus PA. Finally, two separate adiposity models were created due to the high collinearity of BMI and WC. Model four controlled for all variables in model three plus BMI. Model five controlled for all variables in model three plus WC.

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## **Chapter Four: Manuscript**

**SEDENTARY TIME AND CUMULATIVE RISK OF PRESERVED AND  
REDUCED EJECTION FRACTION HEART FAILURE: FROM  
THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS**

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## ABSTRACT

- Purpose:** The purpose of this study was to examine the relationship between self-reported sedentary time (ST) and the cumulative risk of preserved ejection fraction heart failure (HFpEF) and reduced ejection fraction heart failure (HFrEF) using a diverse cohort of U.S. adults 45-84 years of age.
- Methods:** Using data from the Multi-Ethnic Study of Atherosclerosis (MESA), we identified 6,814 subjects (52.9% female). All were free of baseline cardiovascular disease. Cox regression was used to calculate the hazard ratios (HR) associated with baseline ST and risk of overall HF, HFpEF, and HFrEF. Weekly self-reported ST was dichotomized based on the 75<sup>th</sup> percentile (1,890 min/wk).
- Results:** During ~11.2 years of follow-up there were 178 first incident HF diagnoses; 74 HFpEF, 69 HFrEF and 35 with unknown EF. Baseline ST >1,890 min/wk was significantly associated with an increased risk of HFpEF (HR [95% CI]; 1.87 [1.13 – 3.09],  $p = 0.01$ ), but not HFrEF (HR [95% CI]; 1.30 [0.78 – 2.15],  $p = 0.32$ ). The relationship with HFpEF remained significant in separate fully adjusted models including either waist circumference (HR [95% CI]; 2.16 [1.23 – 3.78],  $p < 0.01$ ) or body mass index (HR [95% CI]; 2.17 [1.24 – 3.80],  $p < 0.01$ ). Additionally, every 60 minute increase in weekly ST was associated with a significant 3% increased risk of HFpEF (HR [95% CI]; 1.03 [1.01 – 1.05],  $p < 0.01$ ).
- Conclusions:** Sedentary time >1,890 min/wk (~4.5 h/d) is an independent predictor of HFpEF, but not HFrEF.

## INTRODUCTION

According to 2017 estimates (1), the prevalence of heart failure (HF) among U.S. adults is currently 6.5 million. By 2030, this number is projected to reach 8.5 million, an increase of 46% from 2012 estimates (2). At 45 years of age, the lifetime risk of developing HF ranges from 20 - 45% (3). Presently, the prognosis after being diagnosed with HF is extremely unpromising; approximately 50% of people diagnosed will die within five years (4, 5, 6). In general, HF is a complex clinical syndrome that can result from any cardiac disorder that impairs the ability of the ventricle to function properly (7). The majority of HF cases affect the left ventricle of the heart, and as left-sided HF is the most common cause of right-sided HF, this is the focus of most HF research. Two subtypes of left-sided HF are currently recognized: heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) (7, 8).

According to Yancy et al. (8), HFrEF is defined as an  $EF \leq 40\%$ , HFpEF is an  $EF \geq 50\%$ , and an EF of 41 - 49% is considered borderline HFpEF. This differential diagnosis based on EF is crucial as previous research has demonstrated that the risk factors, pathophysiology, prognosis and response to pharmaceutical and rehabilitative therapy are different among these subtypes (9-14). In HFrEF, myocardial remodeling is driven by cardiomyocyte death due to oxidative stress originating in the cardiomyocytes as a result of ischemia, infection, or toxicity, whereas in HFpEF, comorbidities contribute to a systemic inflammatory state, which induces oxidative stress in the coronary microvascular endothelium (14). Presently, therapeutic strategies that are successful in improving symptoms among those with HFrEF have proven ineffective on patients with HFpEF (9, 10). Therefore, identifying modifiable risk factors, such as sedentary time

(ST), which may play a role in the development of the different subtypes of HF are critical for developing effective prevention strategies.

Sedentary behavior has been defined as any waking behavior characterized by an energy expenditure  $\leq 1.5$  metabolic equivalents (METs), while in a sitting, reclining or lying posture (15). Therefore, ST is the total amount of time spent engaging in sedentary behaviors. This is distinctly different from physical inactivity, defined as an insufficient amount of physical activity (PA) to meet present PA recommendations (16). A recent meta-analysis of 47 studies concluded that self-reported prolonged ST was significantly associated with CVD incidence and CVD mortality (HR [95%CI]; 1.14 [1.00-1.73 and 1.15 [1.11-1.20], respectively) independent of PA (17). Young et al (18) found a significant association between increased ST and HF risk. Additionally, a study by Wijndaele et al (19) observed that television viewing time, a form of ST, was positively associated with incident HF, independent of PA. However, little is known about the relationship between ST and the risk of the different subtypes of HF.

The purpose of this study was to examine the relationship between self-reported ST and the cumulative risk of HFpEF and HFrEF using a diverse, population-based sample of U.S. adults. Based on the inflammatory driven pathophysiology and common cardiometabolic risk factors associated with HFpEF, along with previous research demonstrating a stronger relationship with lower PA and higher BMI and HFpEF (12), we hypothesized that a higher volume of sedentary time would be associated with increased risk of HFpEF, but not HFrEF.



## METHODS

This study analyzed data from the MESA (20), a continuous survey sponsored by the National Heart Lung and Blood Institute of the National Institutes of Health. The MESA is a diverse, population based sample that examines the characteristics of subclinical cardiovascular disease and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease. Details on this study have been published elsewhere (20). In brief, the sample (n= 6,814) consisted of men and women (45-84 years of age) who were free of baseline cardiovascular disease (CVD) upon enrollment. The MESA utilized both physical exams and questionnaires. The first exam took place from July 2000-July 2002, and a total of four additional follow-up exams were completed by 2012. Participants are continuously contacted every 9-12 months to assess clinical morbidity and mortality data. Data from the MESA was requested and obtained from the National Institutes of Health/ National Heart, Lung, and Blood Institute: Biologic Specimen and Data Repository Information Coordinating Center (21). The use of MESA data was approved by the Institutional Review Board of the University of North Florida.

*Dependent Variable:* Heart failure, classified as either definite or probable, was an adjudicated event in MESA determined by a panel of physicians following review of patient medical records. Probable HF was defined as: HF diagnosed by physician and patient receiving medical treatment for HF. Definite HF determination required additional evidence of pulmonary edema or congestion, dilated ventricle, poor left ventricular function, or left ventricular diastolic dysfunction. In the present study, those

with an EF  $\leq$  40% at time of diagnosis were classified as HFrEF, and those with a borderline EF (41 - 49%) or an EF  $\geq$  50% were classified HFpEF.

*Independent Variable:* Self-reported, baseline ST based on the typical week physical activity survey (TWPAS) completed by all MESA participants. The following questions from the survey were used to estimate total weekly sedentary minutes: “In a typical week in the past month, did you sit or recline and watch TV?” and “In a typical week in the past month, did you read, knit, sew, visit, do nothing, non-work recreational computer?” Responses included yes or no, days per week (1 - 7), hours per day (1 - 5 or 5+), and minutes per day (5, 15, 30, or 45). Total hours per day (converted to minutes) and minutes per day were summed and multiplied by days per week to accumulate an estimated minutes per week of ST. Total weekly ST was then used to create two ST variables, one dichotomized at the 75<sup>th</sup> percentile ( $\leq$  or  $>$  1,890 min/wk) and one that represented every 60 minute interval of ST.

*Other independent measures:* Age, sex, race, and smoking status were self-reported at baseline on the personal history form. Hypertension and diabetes were also self-reported at baseline on the medical history form. Metabolic Syndrome was a calculated variable in MESA based on participants’ measured waist circumference, triglycerides, high density lipoprotein cholesterol, blood pressure, and fasting blood glucose. The MESA utilized the National Cholesterol Education Program Guidelines (21) to define metabolic syndrome. The intentional exercise measure using several questions from the TWPAS including walking, sport/dance, and conditioning, reported in MET-minutes per day, was used to determine risk independent of PA. Body mass index (BMI) was calculated as body weight in kilograms (kg) divided by height in meters squared ( $m^2$ )

using measurements obtained at exam one. Waist circumference (WC) was also measured at exam one in centimeters (cm).

*Statistical Analysis:* Data was managed utilizing SAS 9.4 (22) where complex variable recodes, coding verification, and statistical analyses were performed. The means and frequency procedures (PROC MEANS and PROC FREQ) were used to construct a descriptive characteristics table for continuous and categorical variables, respectively. The univariate procedure (PROC UNIVARIATE) was used to determine the 75th percentile of self-reported ST. Separate proportional hazards regression procedures (PROC PHREG) were utilized to calculate multivariable adjusted hazard ratios (HRs) to determine risk of overall HF, HFpEF and HFrEF according to baseline ST. Incident HF without data on ejection fraction were excluded from the HF subtype analysis.

Five separate models were constructed for each of the outcome variables. Model one was unadjusted. Model two controlled for age, sex, race, smoking, hypertension, diabetes, and metabolic syndrome. Model three controlled for all variables in model two plus PA. Finally, two separate adiposity models were created due to the high collinearity of BMI and WC. Model four controlled for all variables in model three, plus BMI. Model five controlled for all variables in model three, plus WC.

## RESULTS

Among the 178 subjects that developed HF, 143 subjects had a known EF at the time of HF diagnosis. Of those, 74 were categorized HFpEF and 69 HFrEF. Table 1 contains the baseline characteristics, including demographics, race, clinical characteristics, and ST according to HFpEF, HFrEF, overall HF and no HF. The

multivariable adjusted HRs derived from the proportional hazards regression procedure for overall HF, HFpEF, and HFrEF are presented in Table 2. While baseline ST > 1,890 min/wk was borderline significant, with a 38% increased risk of overall HF in the unadjusted model (HR [95%CI]; 1.38 [1.00-1.89],  $p=0.05$ ), this relationship was attenuated with further adjustments for demographics, common risk factors, PA, and adiposity measures, and did not remain significant. Baseline ST was not significantly associated with risk of HFrEF in any model.

<b>Table 1. Baseline Characteristics</b>				
<b>Total n = 6,814</b>	<b>HFrEF (n = 69)</b>	<b>HFpEF (n = 74)</b>	<b>Overall HF (n = 178)</b>	<b>No HF (n = 6,636)</b>
<b>Demographics</b>				
Age (years)	68 ( $\pm$ 9.0)	69 ( $\pm$ 8.6)	69 ( $\pm$ 8.7)	62 ( $\pm$ 10.2)
Male	49 (71.0%)	38 (51.4%)	106 (59.6%)	3,107 (46.8%)
<b>Race/Ethnicity</b>				
White	28 (40.6%)	32 (43.2%)	69 (38.8%)	2,553 (38.5%)
African American	28 (40.6%)	18 (24.3%)	61 (34.3%)	1,831 (27.6%)
Hispanic	13 (18.8%)	15 (20.3%)	38 (21.4%)	1,458 (22.0%)
Chinese	0 (0.0%)	9 (12.2%)	10 (5.6%)	794 (12.0%)
<b>Clinical Characteristics</b>				
Heart Rate (bpm)	64 ( $\pm$ 11.5)	64 ( $\pm$ 9.8)	65 ( $\pm$ 11.1)	63 ( $\pm$ 9.6)
BMI (kg/m <sup>2</sup> )	29.2 ( $\pm$ 5.1)	30.3 ( $\pm$ 6.0)	30.2 ( $\pm$ 6.2)	28.3 ( $\pm$ 5.4)
WC (cm)	104.1 ( $\pm$ 18)	105.6 ( $\pm$ 15.1)	105.7 ( $\pm$ 17.3)	98.0 ( $\pm$ 14.3)
Hypertension	51 (73.9%)	58 (78.4%)	135 (75.8%)	2,923 (44.1%)
Metabolic Syndrome	33 (47.8%)	44 (59.5%)	96 (53.9%)	2,353 (35.6%)
Diabetes	19 (27.9%)	25 (33.8%)	56 (31.6%)	717 (10.8%)
Current Smoking	15 (21.7%)	8 (10.8%)	28 (15.7%)	860 (13.0%)
<b>Sedentary Time</b>				
Average (min/week)	1,687.3	1,595.3	1,648.0	1,427.4
$\leq$ 1,890 min/week	45 (66.2%)	50 (67.6%)	119 (67.2%)	5,001 (75.6%)
$>$ 1,890 min/week	23 (33.8%)	24 (32.4%)	58 (32.8%)	1,617 (24.4%)
Values are expressed in mean (SD) for continuous variables and n (%) for categorical variables. Abbreviations: HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; BMI = body mass index (kg/m <sup>2</sup> ); WC = waist circumference (cm).				

<b>Table 2. Hazard Ratios Associated with Sedentary Time (ST) &gt;1,890 min/wk and Risk of Incident Heart Failure</b>						
	<b>Overall HF</b>		<b>HFpEF</b>		<b>HFrEF</b>	
	HR [95% CI]	P-value	HR [95% CI]	P-value	HR [95% CI]	P-value
<b>Model 1</b>	1.38 [1.00-1.89]	0.05	1.87 [1.13-3.09]	0.01	1.30 [0.78-2.15]	0.32
<b>Model 2</b>	1.25 [0.89-1.74]	0.20	1.90 [1.09-3.30]	0.02	1.15 [0.66-2.00]	0.62
<b>Model 3</b>	1.25 [0.90-1.75]	0.19	1.92 [1.10-3.36]	0.02	1.15 [0.66-2.00]	0.63
<b>Model 4</b>	1.25 [0.89-1.75]	0.20	2.16 [1.23-3.78]	< 0.01	1.20 [0.64-2.23]	0.57
<b>Model 5</b>	1.23 [0.88-1.72]	0.24	2.17 [1.24-3.80]	< 0.01	1.18 [0.65-2.15]	0.58
<b>Per 60 min ST</b>	1.01 [1.00-1.02]	0.28	1.03 [1.01-1.05]	< 0.01	1.01 [0.99-1.02]	0.57
Model 1: unadjusted Model 2: adjusted for age, sex, race, smoking, hypertension, diabetes, and metabolic syndrome Model 3: model 2 additionally adjusted for physical activity (METs) Model 4: model 3 additionally adjusted for waist circumference (cm) Model 5: model 3 additionally adjusted for body mass index (kg/m <sup>2</sup> ) Per 60 min ST: adjusted for all variables in model 4 Abbreviations: min/wk= minutes per week; HFpEF= heart failure with preserved ejection fraction; HFrEF= heart failure with reduced ejection fraction; HR= hazard ratio; CI= confidence interval.						

In the unadjusted model, baseline ST > 1,890 min/wk was significantly associated with an 87% increased risk of HFpEF (HR [95% CI]; 1.87 [1.13-3.09]) when compared to those with ST ≤ 1,890 min/wk. The relationship remained significant following adjustment for age, sex, race, smoking, hypertension, diabetes, and metabolic syndrome (HR [95% CI]; 1.90 [1.09-3.30]). The addition of PA (HR [95% CI]; 1.92 [1.10-3.36]), and adiposity measures WC (HR [95% CI]; 2.16 [1.23-3.78]) and BMI (HR [95% CI]; 2.17 [1.24-3.80]) did not attenuate significance. Similarly, when ST was evaluated for every 60 minute increase, a significant relationship was only observed with HFpEF. Every 1 hour increase in weekly ST was associated with a 3% increased risk of HFpEF (HR [95% CI]; 1.03 [1.01-1.05]), independent of all variables in model 4. A 1% increased risk was observed for overall HF that was borderline significant (p= 0.06) in

the crude model, however significance was lost following further adjustment. No such relationship was observed with HFrEF.

## DISCUSSION

In the current study, a statistically significant relationship between a higher volume of ST and risk of HFpEF was observed. Additionally, this relationship remained significant when demographics, several traditional risk factors, intentional exercise, and adiposity measures were added to the model. Furthermore, for every hour of increased weekly ST, a significant 3% increased risk of HFpEF was observed. Borderline significance in the crude model was observed for overall HF, however this was attenuated following further adjustment. No association between ST and risk of HFrEF was detected in any of the models.

Several studies have found an association between higher volumes of ST and increased risk of overall HF (18, 19), however the relationship between ST and the HF subtypes was previously unexplored. Recently, a study by Pandey et al (12) demonstrated an inverse, dose-response relationship between leisure-time PA and risk of overall HF and HFpEF, but not HFrEF. The authors suggested that this association is likely due to the different potential mechanisms in which PA lowers cardiovascular risk and the difference in the pathophysiology of HFpEF and HFrEF. As lower amounts of ST, independent of PA, are also associated with lower cardiovascular risk (17), this rationale could also potentially explain the relationship between HFpEF and ST.

This study adds to the literature by characterizing, for the first time, the positive relationship between ST and risk of HFpEF, independent of intentional exercise and

adiposity. This study suggests that spending  $> 4.5$  h/d sedentary, regardless of intentional exercise or adiposity, significantly increases risk of HFpEF. Reducing ST, along with increasing PA, should be emphasized to prevent the development of HFpEF and should be a therapeutic target to potentially prevent the pathological progression of HFpEF. Future studies should investigate ST objectively, and seek to establish a target goal for ST recommendations for this population.

This study was not without limitations. The use of self-reported baseline ST is subject to recall and self-report bias. Additionally, ST was not objectively measured. The time to the first HF event was used to establish incident HF and EF, therefore subsequent HF events by the same participant or changes in EF measurement over time were not included in the analysis. Baseline ST and PA were examined for all participants, changes in behavior over the timeframe of the study were not taken into consideration for risk determination. Individuals without EF data at the time of the first HF event were not included in the analysis.

In conclusion, ST is positively associated with the cumulative risk of HFpEF. This relationship is independent of demographics, traditional risk factors, intentional exercise, and adiposity measures. This identifies a potential area of intervention for preventing HFpEF and adds to the evidence of HFpEF and HFrEF having separate causal pathways and risk factors.



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## **Appendices**

## Appendix A



UNIVERSITY of  
NORTH FLORIDA.

Office of Research and Sponsored Programs  
1 UNF Drive  
Jacksonville, FL 32224-2665  
904-620-2455 FAX 904-620-2457  
Equal Opportunity/Equal Access/Affirmative Action Institution

### MEMORANDUM

**DATE:** October 24, 2016

**TO:** Ms. Rariden

**VIA:** Dr. James Churilla  
Clinical and Applied Movement Sciences

**FROM:** Dr. Jennifer Wesely, Chairperson  
On behalf of the UNF Institutional Review Board

**RE:** "Relationship between physical activity and incident heart failure in those with preserved and reduced ejection fraction"

This is to advise you the Human Subject Research Determination Form for the project named above was reviewed on behalf of the UNF Institutional Review Board, and has subsequently been granted this waiver of IRB review. As such, this project was declared "not research involving human subjects" based on the federal definition as stated in the U.S. Department of Health and Human Services Code of Federal Regulations [45 CFR 46.102](#). Therefore, it is not necessary for this project to be reviewed and approved by the UNF IRB. However, the principal investigator is not absolved from complying with other federal, state, or local laws or institutional policies and procedures.

Thank you for submitting the HSR Determination Form for IRB consideration. We appreciate that you understand the value of IRB review of human subject research and projects conducted at UNF. Any unanticipated problems involving risk and any occurrence of serious harm to subjects and others shall be [reported](#) promptly to the IRB. This waiver should be kept for your records and applies to your project in the form and content as submitted to the IRB for review. Any variations or modifications to this waived project as related to dealing with human subjects must be cleared with the IRB prior to implementing such changes.

Should you have questions regarding your project or any other IRB items, please contact the research integrity unit of the Office of Research and Sponsored Programs by emailing [IRB@unf.edu](mailto:IRB@unf.edu) or calling (904) 620-2455.

This letter has been electronically signed in accordance with all applicable regulations, and a copy is retained within UNF's records.

## Appendix B

### NHLBI Research Materials Distribution Agreement (RMDA)

#### Introduction and Definitions

The National Heart, Lung, and Blood Institute (NHLBI), the RECIPIENT Organization (RECIPIENT) and the Principal Investigator (PI) hereby enter into this Research Materials Distribution Agreement (RMDA) as of the effective date specified on the final signature page.

The Research Materials and Research Plan covered by this RMDA are:

- Name of Clinical Study: MESA
- Title of Research Plan: RELATIONSHIP BETWEEN SELF-REPORTED PHYSICAL ACTIVITY AND CUMULATIVE RISK OF PRESERVED AND REDUCED EJECTION FRACTION HEART FAILURE (THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS).
- Research Materials Requested: Data
- Research Plan Includes a Commercial Purpose: No
- Name of Principal Investigator (PI): James R. Churilla, Ph.D., MPH, MS, FACSM
- Email of Principal Investigator (PI): jchurilla.80821@unf.edu
- Name of Other Approved Users at PI's Institution: Brandi Kariden

The Research Materials are provided through the Biologic Specimen and Data Repository Information Coordinating Center. The Center was established by the NHLBI to develop and maintain the infrastructure necessary to facilitate and maximize access to Research Materials from NHLBI-sponsored studies in accordance with NHLBI approved procedures.

The Research Materials were collected as part of the above clinical study, hereafter referred to as "STUDY". They constitute a unique scientific resource and the NHLBI is committed to making them available in a timely manner, on appropriate terms and conditions, to the largest possible number of qualified investigators who wish to analyze the materials in a secondary study designed to enhance the public health benefit of the original work. The RECIPIENT and PI acknowledge responsibility for ensuring the review of and agreement to the terms within this RMDA and the appropriate research use of the Research Materials, subject to applicable laws and regulations.

The RECIPIENT and PI acknowledge that other researchers are entitled to access to the Research Materials on the same terms as RECIPIENT so that duplication of research may occur. RECIPIENT and PI also recognize that the STUDY Investigators have made a substantial long-term contribution in establishing the Research Materials and the NHLBI encourages appropriate collaborative relationships by outside investigators with the STUDY Investigators and proper acknowledgement of their contributions.

The NHLBI believes that the confidentiality and privacy of the STUDY participants can best be assured by requiring all who are interested in accessing the Research Materials to acknowledge their review of this RMDA and agree to adhere to its provisions. Violation of its confidentiality provisions could lead to legal action on the part of STUDY participants, their families, or the U.S. Government.

Note: RECIPIENT requests access to NHLBI Research Materials for its PI at its sole risk.

For the purpose of this Agreement:

"RECIPIENT" is any organization that is seeking access to STUDY Research Materials, and may be a: Public/State Controlled Institution of Higher Education; Private Institution of Higher Education; Nonprofit organization with 501(c)(3) IRS Status (Other than Institution of Higher Education); Nonprofit Organization without 501(c)(3) IRS Status (Other than Institution of Higher Education); Small Business; For-Profit Organization (Other than Small Business); State Government; Government of a U.S. Territory or Possession; Non-domestic (non-U.S.) Entity (Foreign Organization); or Eligible Agency of the U.S. Government.

"Principal Investigator (PI)" is an individual judged by the RECIPIENT to have the appropriate level of authority and responsibility to lead the scientific investigation proposed in the Research Plan using the requested materials, oversee the supporting staff who are provided access to the Research Materials and contribute to the analytic effort and public disclosure of STUDY results, and assume responsibility for all team members' compliance with the terms and conditions of this RMDA.

"APPROVED USERS" are all individuals specifically identified in the Research Plan, including the PI. Only individuals listed in the Research Plan may have access to the Research Materials.

"Research Plan" is a description of the proposed research that includes the identities of the investigators participating in the research effort. The Research Plan must include the project title, the RECIPIENT's name, the PI's name, the name of other APPROVED USERS, and the proposed research protocol with the research objectives and design. For plans including biospecimens, the biospecimen material type, number, minimum volume, and required characteristics needed to meet the objectives of the protocol must also be included.

"Research Materials" are the requested materials covered by this RMDA and may include STUDY data, defined as clinical or epidemiologic subject data, and/or STUDY biospecimens. STUDY biospecimens may have associated characterization data. Characterization data serve to describe STUDY biospecimens only and are not considered to be STUDY data; they are exempt from STUDY data requirements that may be described elsewhere in this RMDA.

"STUDY" is the clinical study that collected the Research Materials described in this RMDA.

"STUDY Investigator" is a research investigator with a current or previous grant, contract or consulting agreement with the NHLBI, or one of its contractors, to work on the STUDY.

#### Terms of Access

##### 1. Research Use

The RECIPIENT and APPROVED USERS agree that they will use the Research Materials solely in connection with the research project described in the Research Plan named in this RMDA. Substantive modifications to the research project will require submission of a revised

BiLINCC RMDA V02 1d20120806	Page 1	Date Generated: 20161216
Name of Principal Investigator: James R. Churilla, Ph.D., MPH, MS, FACSM		
Title of Research Plan: RELATIONSHIP BETWEEN SELF-REPORTED PHYSICAL ACTIVITY AND CUMULATIVE RISK OF PRESERVED AND REDUCED EJECTION FRACTION HEART FAILURE (THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS).		

## RMDA.

### 2. Institutional and Approved User Responsibilities

RECIPIENT and APPROVED USERS acknowledge that RECIPIENT's Institutional Review Board (IRB) has reviewed the Research Plan and either approved it or determined that it is exempt from review. Access to Research Materials from some STUDIES requires IRB approval and/or compliance with other limitations, and RECIPIENT agrees to abide by all such conditions and limitations on the Research Materials. RECIPIENT certifies that its IRB is operating under an Office of Human Research Protections (OHRP) - approved Assurance and in accordance with Department of Health and Human Services regulations at 45 CFR Part 46. RECIPIENT and APPROVED USERS agree to comply fully with all such conditions.

RECIPIENT and APPROVED USERS agree to report promptly to the NHLBI any proposed change in the Research Plan and any unanticipated problems involving risks to subjects or others. Changes to the Research Plan include changes in the APPROVED USERS list. This RMDA is made in addition to, and does not supersede, any of RECIPIENT's institutional policies or any local, State, and/or Federal laws and regulations that provide additional protections for human subjects.

Evidence of local IRB review and/or approval (where appropriate) from an expedited or convened review to conduct the Research Plan with the requested STUDY data must be included in a supplemental Adobe PDF document that will be uploaded during the application process and attached to the RMDA form.

### 3. Public Posting of Approved User's Research Use Statement

The RECIPIENT and PI agree that information about the proposed research use can be posted on a public web site that describes the project(s) included in the Research Plan. The information will include the PI's name, RECIPIENT institution, project title, and a brief summary of the research. In addition, citations resulting from the use of Research Materials may be posted on the Biologic Specimen and Data Repository Information Coordinating Center Website.

### 4. Non-Identification

The PI agrees not to use the Research Materials, either alone or in concert with any other information, to identify or contact individual STUDY subjects without specific approval to contact STUDY subjects obtained from the IRB(s) responsible for the STUDY.

### 5. Non-Transferability of Research Materials

The RECIPIENT and PI agree to retain control over the Research Materials, and further agree not to release or distribute Research Materials in any form to any entity or individual unless required by NHLBI policies. The RECIPIENT and PI agree to store Research Material data on a computer with adequate security controls (see Section 6), and to maintain appropriate control over the Research Materials at all times. Research Materials data containing individual-level information, in whole or in part, may not be sold to any entity or individual at any point in time for any purpose.

The PI agrees that if his or her relationship with the RECIPIENT terminates and a relationship with a different RECIPIENT is established during the period of the RMDA, a new RMDA from the second RECIPIENT will be submitted and approved before the PI resumes use of the Research Materials. Any versions of Research Material data stored at the first RECIPIENT will be destroyed and their destruction documented. However, if advance written notice and approval by the NHLBI Program Office is obtained to transfer responsibility for the approved Research Plan to a different PI with a relationship with the first RECIPIENT, the Research Material data may not need to be destroyed.

### 6. Security of Research Materials

The RECIPIENT and PI agree to store Research Material data on a computer with security controls adequate to protect sensitive or identifiable information, to ensure that only approved, supervised persons have access to the data, and to maintain appropriate control over the Research Materials at all times. Hard copies of any Research Material must similarly be stored under conditions sufficiently secure to avoid inappropriate access, and shredded prior to discarding.

This RMDA will be in effect for a period of three (3) years from its effective date for the requested STUDY data set. At the end of the three (3) year period, the RECIPIENT and PI agree to destroy all copies of the STUDY data, and all derivatives that contain individual-level information. Characterization data associated with the STUDY biospecimens are exempt from this requirement.

An extension of this RMDA may be permitted by the NHLBI upon submission by the PI and RECIPIENT of evidence of IRB approval for the extended period.

### 7. Intellectual Property

By requesting access to the STUDY Research Materials, the REQUESTER and APPROVED USERS acknowledge the intent of the NHLBI to see that anyone authorized for research access through the attached Research Plan, follow the intellectual property principles within the NIH GWAS Policy for Data Sharing as summarized below:

Achieving maximum public benefit is the ultimate goal of Research Material distribution through the NHLBI Biological and Data Repository Information Coordinating Center. The NIH believes that Research Materials, such as these covered by this RMDA, should be considered as pre-competitive, and urges APPROVED USERS to avoid making IP claims derived directly from the STUDY Research Materials. However, the NIH also recognizes the importance of the subsequent development of IP on downstream discoveries, especially in therapeutics, which will be necessary to support full investment in products to benefit the public.

It is expected that these NHLBI-provided data, and conclusions derived there from, will remain freely available, without requirement for licensing. The NIH encourages broad use of shared Research Materials coupled with a responsible approach to management of intellectual property derived from downstream discoveries in a manner consistent with the NIH's Best Practices.

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Name of Principal Investigator: James R. Churilla, Ph.D., MPH, MS, FACSIM		
Title of Research Plan: RELATIONSHIP BETWEEN SELF-REPORTED PHYSICAL ACTIVITY AND CUMULATIVE RISK OF PRESERVED AND REDUCED EJECTION FRACTION HEART FAILURE (THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS).		



for the Licensing of Genomic Inventions and the NIH Research Tools Policy.

#### 8. Acknowledgement of BioLINCC Research Resources

RECIPIENT agrees to acknowledge the contribution of the STUDY in all oral and written presentations, disclosures, or publications resulting from any analyses conducted on the STUDY Research Materials.

If the Research Plan involves collaboration with STUDY Investigators, then the APPROVED USERS will comply with all policies established by the STUDY's publications committee. In addition, the APPROVED USERS will acknowledge the source of the data by including language similar to the following either in the acknowledgment or in the text of the manuscript: "This manuscript was prepared using MESA Research Materials obtained from the NHLBI."

If the Research Plan does not involve collaboration with STUDY Investigators or the STUDY has ended, the RECIPIENT will acknowledge the source of the data by including language similar to the following either in the acknowledgment or in the text of the manuscript: "This Manuscript was prepared using MESA Research Materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the MESA or the NHLBI." Manuscripts and abstracts resulting from the Research Plan should not use the name of the STUDY in the title of the manuscript/abstract unless the title clearly denotes the source of the Research Materials as being from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center (e.g., "An Investigation using the <STUDY name and Research Materials>"). The purpose is to delineate manuscripts from the Research Plan and APPROVED USERS from manuscripts from the STUDY and STUDY Investigators.

The RECIPIENT and PI agree to ensure that all APPROVED USERS will not include in any manuscripts derived from Research Materials any case studies that describe the characteristics of individual participants, or a small number or groups of participants.

#### 9. Research Use Reporting

Prompt publication or other public disclosure of the results of the Research Plan is encouraged.

When requested by the NHLBI, the APPROVED USERS agree to provide general comments regarding topics such as the effectiveness of the NHLBI Biological Specimen and Data Repository Information Coordinating Center Research Material access process (ease of access and use; appropriateness of STUDY data format; challenges in following the policies; suggestions for improving research material access; or the program in general).

#### 10. Non-Endorsement, Indemnification

The RECIPIENT and PI acknowledge that although all reasonable efforts have been taken to ensure the accuracy and reliability of Research Materials, the NHLBI and STUDY Investigators do not and cannot warrant the results that may be obtained by using any Research Materials included therein. The NHLBI and all contributors to these Research Materials disclaim all warranties as to performance or fitness of the Research Materials for any particular purpose.

No Indemnification for any loss, claim, damage or liability is intended or provided by any party under this Agreement. Each party shall be liable for any loss, claim, damage, or liability that said party incurs as a result of its activities under this Agreement, except that the NIH, as an agency of the United States, assumes liability only to the extent provided under the Federal Tort Claims Act, 28 U.S.C. 2671 et seq.

#### 11. Termination and Violations

The NHLBI may terminate this Agreement if RECIPIENT or APPROVED USERS are in default of any of its conditions and such default has not been remedied within 30 days after the date of written notice of such default by an authorized representative of the NHLBI. Past violations will be taken into consideration by the NHLBI for future requests from the RECIPIENT and APPROVED USERS to access NHLBI Research Materials.

#### 12. Amendments

Amendments to this Agreement must be made in writing and signed by authorized representatives of all parties.

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Name of Principal Investigator: James R. Churilla, PhD, MPH, MS, FACS		
Title of Research Plan: RELATIONSHIP BETWEEN SELF-REPORTED PHYSICAL ACTIVITY AND CUMULATIVE RISK OF PRESERVED AND REDUCED EJECTION FRACTION HEART FAILURE (THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS)		



### Signatures Page

By submission of the RMDA, the RECIPIENT and PI attest to the APPROVED USERS qualifications for access to and use of STUDY Research Materials and certify their Agreement to the NHLBI principles, policies, and procedures for the use of Research Materials as articulated in this document.

This Agreement is entered into as of: 1-9-17 (effective date)

#### BY RECIPIENT:

Name of RECIPIENT Institution: University of North Florida

Name and Title of RECIPIENT's Authorized Institutional Business Official: John Kantner  
Associate VP for Research

Signature and Date of RECIPIENT's Authorized Institutional Business Official: [Signature] 1/9/17

E-Mail address of Authorized Institutional Business Official: J.KANTNER@UNF.EDU

#### BY PRINCIPAL INVESTIGATOR:

Name: James R. Churilla, Ph.D., MPH, MS, FACS

Title: Associate Professor - Graduate Program Director

Surface Mail Address: 1 UNF Drive - Jacksonville, FL 32224

E-Mail Address: jchurilla.BOB21@unf.edu

Telephone Number: \_\_\_\_\_

Fax Number: 6 \_\_\_\_\_

Signature and Date: [Signature] 1-9-17

#### BY NHLBI Authorized Representative:

Name and Title:

Sean A.

Coady -S

Signature and Date:

Digitally signed by Sean A. Coady -S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=NIH, ou=People,  
cn=Sean A. Coady -S,  
0.9.2342.19200300.100.1.1=0010154  
059  
Date: 2017.01.13 08:43:04 -05'00'

"Authorized Institutional Business/Signing Official" is an individual with the authority to enter into business transactions on behalf of the RECIPIENT.

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Name of Principal Investigator: James R. Churilla, Ph.D., MPH, MS, FACS		
Title of Research Plan: RELATIONSHIP BETWEEN SELF-REPORTED PHYSICAL ACTIVITY AND CUMULATIVE RISK OF PRESERVED AND REDUCED EJECTION FRACTION HEART FAILURE (THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS).		

## Appendix C

### Thesis Committee Membership Form

This completed form should be submitted to the Office of the Dean of the Graduate School at the time the thesis committee is established. This form may be submitted multiple times.

Date: Jan 17, 2018 Student Name: Brandi Rariden N#: 00774738

Program: Exercise Science and Chronic Disease College: Brooks College of Health

Form Type: Initial ☒ Change ☐

Thesis Title: Sedentary time and cumulative risk of preserved and reduced ejection fraction heart failure: from the multi-ethnic study of atherosclerosis

Committee Members: (All committee members must be listed. If a committee member is Non-Graduate Faculty, the Request for Non-Graduate Faculty Thesis Form is required. If a committee member is a non-UNF faculty member, the Request for External Thesis Committee Member is required.)

Committee Member/N#	Chair	Department/Program	Graduate Faculty Status	
Dr. James Churilla	<input checked="" type="checkbox"/>	CAMS	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
Dr. Sherry Pinkstaff	<input type="checkbox"/>	CAMS	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
Dr. Tammie Johnson	<input type="checkbox"/>	Public Health	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
Mr. Ryan Richardson	<input type="checkbox"/>	CAMS	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
Dr. Clinton Brawner	<input type="checkbox"/>	External	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>

Is this committee complete? Yes ☒ No ☐

**Institutional Review Board/Institutional Animal Care and Use Committee Understanding:** We the undersigned understand that if proposed research for any thesis or dissertation is subject to the federal regulations pertaining to research involving either human or animal subjects, review by the UNF Institutional Review Board (IRB) and/or UNF Institutional Animal Care and Use Committee (IACUC) must be obtained prior to beginning such research. The measures taken to ensure the protection of human and/or animal subjects should be explicitly addressed in the researcher's discussion of methodology when applicable.

Committee Chair Signature/Date

Program Chair Signature/Date

Department Chair Signature/Date

**For Graduate School Office Use:**

OFFICIAL  
Received

JAN 17 2018

The Graduate School

Updated: 3/9/2016

### **Vita**

Brandi S. Rariden is a graduate teaching and research assistant in the Clinical and Applied Movement Sciences department at the University of North Florida (UNF) in Jacksonville, FL. There, she recently completed her master's degree in Exercise Science and Chronic Disease. Upon earning her Bachelor of Science in Health degree from UNF in 2016, where she majored in Exercise Science and graduated with Magna Cum Laude honors, she completed an internship at Orange Park Medical Center in the Cardiopulmonary Rehabilitation Center and successfully obtained certification as an Exercise Physiologist from the American College of Sport's Medicine.

Originally from a small town in southern Illinois, Brandi currently lives in Orange Park, FL with her husband, Justin, and their three young daughters, Joscelyn, Scarlet, and Peyton. Her research interests consist of cardiovascular health, heart failure, sedentary behavior, and physical activity. Her future ambitions include attending physician assistant school to specialize in cardiovascular medicine.